(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 August 2002 (08.08.2002)

PCT

(10) International Publication Number
WO 02/060442 A1

(51) International Patent Classification[7]: A61K 31/4188, 31/437, C07D 471/04, A61P 1/00

(21) International Application Number: PCT/SE02/00164

(22) International Filing Date: 30 January 2002 (30.01.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0100295-5 1 February 2001 (01.02.2001) SE

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL FORMS OF 2,3-DIMETHYL-8-(2-ETHYL-6-METHYLBENZYLAMINO)-IMIDAZO (1,2-A)PYRIDINE-6-CARBOXAMIDE

(57) Abstract: The present invention relates to novel forms of 2, 3-dimethyl-8-(2-ethyl-6-methylbenzylamino-imidazo[1, 2-a]pyridine-6-carboxamide hydrochloride salt. Further, the present invention also relates to use of said compounds for the treatment of gastrointestinal disorders, pharmaceutical compositions containing them and processes for obtaining them.

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Novel forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo (1,2-a)pyridine-6-carboxamide

Field of the invention

The present invention relates to novel crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt. Further, the present invention also relates to use of said compounds for the treatment of gastrointestinal disorders, pharmaceutical compositions containing them and processes for obtaining them.

Background of the invention and prior art

In the formulation of drug compositions, it is important for the active pharmaceutical ingredient (API) to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations (e.g. oral dosage forms such as tablets) comprising the active pharmaceutical ingredient.

Further, in the manufacture of oral drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of the active pharmaceutical ingredient is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active pharmaceutical ingredient are also very important factors. The active pharmaceutical ingredient, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the physico-chemical characteristics of the active pharmaceutical ingredient, e.g. its chemical composition, density, hygroscopicity and solubility.

Amorphous materials may present problems in this regard. For example, such materials are typically more difficult to handle and to formulate, provide for unreliable dissolution, and are often found to be more unstable.

Thus, in the manufacture of commercially viable and pharmaceutically acceptable drug compositions, it is important, wherever possible, to provide the active pharmaceutical ingredient in a substantially crystalline and stable form.

International patent applications WO 99/55705 and WO 99/55706 discloses a number of compounds, referred to as imidazo pyridine derivatives, which are reversible acid pump inhibitors.

WO 99/55706 also contains a specific disclosure of the compound 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide. A process for the synthesis of this compound is described in Example 1.4 of WO 99/55706, where the compound is crystallized from ethyl acetate.

WO 99/55706 contains no information about the corresponding hydrochloride salt of 2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide. WO 99/55706 does further not disclose how different crystal forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride may be obtained and does not predict the properties of such crystal forms.

Brief description of the drawings

Figure 1 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A.

Figure 2 is an X-ray powder diffractogram of di [2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrochloride salt form B.

Figure 3 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form C.

Figure 4 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form D.

Figure 5 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form E.

Figure 6 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form F.

Figure 7 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt n-propanol solvate.

Figure 8 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt aceton solvate.

Figure 9 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt etanol solvate.

Description of the invention

It has surprisingly been found that 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo-[1,2-a]pyridine-6-carboxamide hydrochloride salt can exist in more than one crystal form. The compounds are hereinafter referred to as 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt forms A to F. The notation A to F relates to the order in time in which the forms were created, not to their relative thermodynamic stability.

It is thus an object of the present invention to provide crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride saltswith advantageous properties.

It is an aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 1, exhibiting substantially the following d-values and intensities;

Form A		Form A		Form A	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
11.3	vs	4.86	m	3.41	m
10.1	s	4.73	w	3.33	m
9.7	vs	4.58	w	3.14	m
9.4	s	4.44	m	3.08	m
8.3	m	4.29	w	3.01	w
7.1	vs	3.99	w	2.90	w
6.5	m	3.95	m	2.76	m
5.9	m	3.86	m	2.70	w
5.5	s	3.70	m	2.64	m
5.3	m	3.54	m	2.55	w
5.1	w	3.45	s	2.50	w

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A. The relative intensities are less reliable and instead of numerical values the following definitions are used;

% Relative Intensity*	Definition
25-100	vs (very strong)
10-25	s (strong)
3-10	m (medium)
1-3	w (weak)

* The relative intensities are derived from diffractograms measured with variable slits.

The definition above has also been used when identifying the peaks of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form B to F, *vide infra*.

Differential Scanning Calorimetry (DSC) on form A showed a single melting endotherm with extrapolated onset of ca 247°C.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide di [2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrochloride salt form B.

Di [2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrochloride salt form B, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 2, exhibiting substantially the following d-values and intensities;

Form B		**Form B**		**Form B**	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
14.2	s	5.8	s	3.93	s
11.2	m	5.7	s	3.80	s
10.1	s	5.6	s	3.68	vs
9.4	vs	5.5	s	3.66	vs
8.9	vs	5.4	m	3.58	vs
8.5	vs	5.1	s	3.38	vs
7.9	m	4.59	m	3.23	vs
7.2	vs	4.43	vs	3.11	s
6.8	vs	4.38	s	3.03	m
6.5	vs	4.33	vs		
6.0	vs	4.26	s		

Differential Scanning Calorimetry (DSC) on form B showed DSC onset 241 °C.

Di [2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrochloride salt form B is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form C.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form C, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 3, exhibiting substantially the following d-values and intensities;

Form C		**Form C**		**Form C**	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
13.1	vs	5.0	m	3.57	m
8.3	vs	4.59	s	3.52	m
8.0	s	4.39	m	3.43	s
7.1	s	4.27	m	3.40	s
6.8	m	4.14	m	3.32	s
6.6	vs	3.95	s	3.27	m
5.9	w	3.81	m	3.06	m
5.8	m	3.71	m	2.95	m
5.2	w				

Differential Scanning Calorimetry (DSC) on form C showed DSC onset 237, 244 °C

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form C is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt Form D.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt Form D, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 4, exhibiting substantially the following d-values and intensities;

Form D		Form D		Form D	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
16.0	vs	5.3	w	3.56	m
14.1	w	5.2	m	3.44	w
9.5	m	4.84	m	3.39	m
8.5	m	4.65	m	3.27	w
7.8	s	4.23	w	3.21	w
7.7	m	4.11	m	3.01	w
7.5	w	4.00	w	2.98	w
7.1	m	3.88	m	2.80	w
6.8	m	3.83	m	2.74	w
6.5	w	3.72	w	2.67	w
6.0	m	3.62	s	2.61	w

Differential Scanning Calorimetry (DSC) on the form D showed DSC onset 210°C and 230°C.

TGA showed an decrease in mass of approximately 3.5%, by weight.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form D is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form E.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form E, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 5, exhibiting substantially the following d-values and intensities;

Form E		Form E	
d value (Å)	Relative intensity	d value (Å)	Relative intensity
14.0	vs	4.31	w
13.2	s	4.15	vw
9.0	vw	4.00	vw
8.3	w	3.51	w
7.9	m	3.43 (3.433)	m
7.5	vw	3.43 (3.426)	m
7.0	vs	3.17	vw
6.6	m	2.99	vw
5.3	w	2.80	vw
5.0	vw	2.75	vw
4.68	w	2.34	w

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form E is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form F.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form F, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 6, exhibiting substantially the following d-values and intensities;

Form F		Form F		Form F	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
12.7	m	5.1	m	3.46	m
11.0	vs	4.72	w	3.41	m
10.1	vs	4.44	w	3.38	m
8.3	s	4.30	w	3.32	s
7.0	m	4.16	s	3.22	m
6.8	m	4.12	m	3.05	m
6.7	m	4.09	m	2.77	m
6.0	m	3.97	w		
5.5	s	3.88	m		
5.4	s	3.68	m		
5.3	m	3.61	m		

Differential Scanning Calorimetry (DSC) on the methanol water solvate showed DSC onset 126°C, 142°C, 151°C, and 167°C.

TGA showed an decrease in mass of approximately 4.8%, by weight.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form F is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt n-propanol solvate.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt n-propanol solvate, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 7, exhibiting substantially the following d-values and intensities;

n-propanol solvate		n-propanol solvate		n-propanol solvate	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
12.6	vs	4.34	w	3.24	s
9.8	vs	4.00	m	3.11	m
9.7	vs	3.94	s	2.77	m
6.7	vs	3.80	m	2.70	m
6.5 (6.55)	s	3.70	m	2.60	w
6.5 (6.48)	m	3.66	s	2.55	w
6.3	s	3.58	m	2.44	w
4.93	vs	3.52	m	2.30	w
4.84	m	3.44	m		
4.54	m	3.34	m		

Differential Scanning Calorimetry (DSC) on the n-propanol solvate showed DSC onset 163 °C

TGA showed a weight loss of approximately 0.96 eq. n-propanol, which was confirmed by NMR.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt n-propanol solvate is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt acetone solvate.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt acetone solvate, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 8, exhibiting substantially the following d-values and intensities;

Acetone solvate		Acetone solvate		Acetone solvate	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
12.6	m	4.34	w	3.23	m
9.8	vs	4.25	w	3.16	w
7.9	m	4.20	w	3.08	w
6.6	s	4.07	m	3.02	m
6.5	m	3.97	m	2.89	w
6.3	m	3.92	m	2.85	w
5.4	w	3.79	w	2.70	m
5.2	w	3.71	w	2.65	w
5.1	m	3.67	s	2.59	w
4.90	s	3.59	w	2.52	w
4.80	m	3.50	m	2.48	w
4.57	w	3.41	m	2.44	w
4.53	m	3.34	m	2.42	w

Differential Scanning Calorimetry (DSC) on the acetone solvate showed DSC onset 159 °C

TGA showed a weight loss of approximately 1.02 eq. acetone, which was confirmed with NMR.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt acetone solvate is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt ethanol solvate.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt ethanol solvate, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 9, exhibiting substantially the following d-values and intensities;

Ethanol solvate		Ethanol solvate		Ethanol solvate	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
12.5	vs	4.54	m	3.40	m
10.4	m	4.22	m	3.31	s
9.7	vs	4.04	m	3.20	s
7.8	m	4.00	m	3.15	m
6.6	vs	3.95	m	3.09	m
6.4	m	3.89	s	3.06	m
6.3	m	3.76	m	2.84	m
5.2	m	3.69	m	2.73	m
5.0	m	3.62	vs	2.70	m
4.87	s	3.55	m	2.57	m
4.77	m	3.48	m	2.51	m

Differential Scanning Calorimetry (DSC) on the ethanol solvate showed DSC onset 147 °C

TGA showed an decrease in mass of approximately 0.96 eq. ethanol, weight loss was confirmed by NMR.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt ethanol solvate is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is possible to crystallize 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salts, i.e. the compounds of the present invention, in one single solvent or in a mixture of solvents. However, we prefer that the crystallization is from one single solvent.

Crystallization of compounds of the present invention from an appropriate solvent system, containing at least one solvent, may be achieved by attaining supersaturation in a solvent system by solvent evaporation, by temperature decrease, and/or via the addition of anti-solvent (i.e. a solvent in which the compounds of the invention are poorly soluble).

Crystallization may also be initiated and/or effected with or without seeding with crystals of the appropriate crystalline compound of the invention.

Crystallization of compounds of the present invention can be achieved starting from pure 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or mixtures of any form.

Whether an anhydrate or a solvate crystallizes is related to the kinetics and equilibrium conditions of the respective forms at the specific conditions. Thus, as may be appreciated by the skilled person, the crystalline form that is obtained depends upon both the kinetics and the thermodynamics of the crystallization process. Under certain thermodynamic conditions (e.g. solvent system, temperature, pressure and concentration of compound of the invention), one crystalline form may be more stable than another (or indeed any other). However, crystalline forms that have a relatively low thermodynamic stability may be kinetically favored. Thus, in addition, kinetic factors, such as time, impurity profile, agitation, the presence or absence of seeds, etc. may also influence which form that crystallizes.

According to the invention there is further provided a process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt forms A to F.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A is obtained upon suspending from ethyl acetate.

Di [2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrochloride salt form B is obtained upon crystallization from water.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form C is obtained upon crystallization from butanol.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form D is obtained upon crystallization from methanol/water (5:7, by volume).

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form E is obtained upon crystallization from methanol.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form F is obtained upon crystallization from methanol/water (1;1, by volume).

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt n-propanol solvate is obtained upon crystallization from n-propanol.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt acetone solvate is obtained upon crystallization from acetone.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt ethanol is obtained upon crystallization from ethanol.

The preparation and characterization of different forms of compounds of the invention are described hereinafter. Different crystalline forms of the compounds of the invention may be readily characterized using e.g. X-ray powder diffraction (XRPD) methods or Raman spectroscopy.

In order to ensure that a particular crystalline form is prepared in the absence of other crystalline forms, crystallization is preferably carried out by seeding with seed crystals of the desired crystalline form. This applies particularly to each of the specific crystalline forms which are described in the Examples.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A is a crystalline form exhibiting advantageous properties, such as being well-defined, being thermodynamically more stable (and less hygroscopic) than other crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt, especially at room temperature. Other crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt can under certain conditions, completely or partly, be converted into form A. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-

a]pyridine-6-carboxamide hydrochloride salt form A is thereby characterized in being thermodynamically more stable than other crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt. Other crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt can therefore be used as intermediates for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A.

Examples of other forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt include, but are not limited to, anhydrates, hydrates, solvates, amorphous forms, and other polymorphs, of which some may be more or less crystalline.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt forms A-F obtained according to the present invention is substantially free from other crystal and non-crystal forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt. The term "substantially free from other crystal and non-crystal forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt" shall be understood to mean that the desired crystal form of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt contains less than 50%, preferably less than 10%, and more preferable less than 5% of any other forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt.

In accordance with the invention, the compounds of the invention may be administered and used as described in WO 99/55705 and WO 99/55706, the content of which is hereby incorporated by reference.

The compounds of the invention may be further processed before formulation into a suitable pharmaceutical formulation. For example, the crystalline form may be milled or ground into smaller particles.

According to a further aspect of the invention, there is provided a pharmaceutical formulation including a compound of the invention in admixture with at least one pharmaceutically acceptable adjuvant, diluent or carrier.

According to a further aspect of the invention there is provided a method of treatment of a condition where inhibition of gastric acid secretion is required or desired, which method includes administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment.

For the avoidance of doubt, by "treatment" we include the therapeutic treatment, as well as the prophylaxis, of a condition.

The compounds of the invention have the advantage that they are in a form that provides for improved ease of handling. Further, the compounds of the invention have the advantage that they may be produced in forms that have improved chemical and solid state stability as well as lower hygroscopicity. Thus, the compounds may be stable when stored over prolonged periods.

The invention is illustrated, but in no way limited, by the following examples.

Examples

General Procedures

X-ray powder diffraction (XRPD) analysis was performed on samples prepared according to standard methods, for example those described in Giacovazzo, C. et al (1995), Fundamentals of Crystallography, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), Introduction to X-Ray Powder Diffractometry, John Wiley & Sons, New York; Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), X-ray Diffraction Procedures, John Wiley and Sons, New York. X-ray analyses were performed using a Siemens D5000 diffractometer and/or a Philips X'Pert MPD.

Differential scanning calorimetry (DSC) was performed using a Mettler DSC820 instrument, according to standard methods, for example those described in Höhne, G. W. H. et al (1996), Differential Scanning Calorimetry, Springer, Berlin.

Thermogravimetric analysis (TGA) was performed using a Mettler Toledo TGA850 instrument.

DSC onset temperatures may vary in the range ±5°C (e.g. ±2°C), and XRPD distance values may vary in the range ±2 on the last decimal place. It should be understood that the d-values of X-ray powder diffraction pattern exhibits variation depending on e.g. equipment used, sample preparation, and operator. However the precision and repeatability of said technique is found to be high and thus X-ray powder diffraction pattern exhibiting substantially the same d-values should be obtained if repeated.

Example 1

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride Form A

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide (57.61 g, 0.17 mol) was dissolved in 1-butanol (850 ml) and heated to 60°C. At 60°C hydrogenchloride gas (40 g, 10 eq.) was added through a dip pipe. The solution was cooled to 5°C and stirred overnight. During stirring overnight, a solid precipitated. The solid was filtered off and washed with 1-butanol (50 ml). The solid was dried at 45°C / 1 mbar for 20 h. Yield was 59.99 g. The material was suspended in ethyl acetate (400 ml) and heated to reflux. After cooling to room temperature the solid was filtered and washed with ethyl acetate (150 ml). The solid was dried at 45°C / 0.3 mbar for 25 h. Yield: 52.41g,

Example 2

Preparation of di [2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrocloride form B

To a solution of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide (3.4 g, 0.01 mol) in 50 ml boiling ethanol a solution of 0.86 g acetylchloride dissolved in 10 ml ethanol was added. The solution was stirred over night at room

temperature. The reaction mixture was cooled on ice and filtered, the crystals was washed with cold ethanol. Yield 0.9 g.

The crystals were suspended in 100 ml boiling acetonitrile, cooled and filtered. Yield 0.86 g.

The crystals were suspended in 20 ml water. During 15 min reflux the crystals first dissolves and then the final product crystallises. The crystals are cooled first in room temperature and then on ice water. The crystals are filtered and washed with water. Yield 0.59 g

Example 3

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C

To a refluxing solution of 1.7 g 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide in 10 ml 2-propanol, a solution of acetylchloride (1 ekv) in 15 ml 2-propanol was added. The HCl salt was precipitating. The product was filtered and washed with 2-propanol. Yield 1.4 g. NMR ½ eqv IPA. The product was refluxed and dissolved in 15 ml butanol. During reflux the crystals first dissolved and then crystallised again. The suspension was stirred at 80 °C for 1 hour. The mixture was left at room temperature to cool. The crystals were filtered off and washed with butanol and ether. The crystals were dried in vacuum at 65 °C for 30 min. Yield 0.85 g.

Example 4

Preparation of an n-propanol solvate

200 mg of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide was refluxed in 4 ml n-propanol until dissolved. 80 mg pyridine hydrochloride was added. The temperature was lowered to 85 °C and seeds of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride was added. The crystallisation starts immediately. The temperature was raised to 95 °C for 1 h. The stirred suspension was then left at 80 °C for 16 h. The mixture was allowed to cool to room temperature and then filtered and the crystals were washed with n-propanol. Yield 226 mg.

Example 5

Preparation of an acetone solvate

200 mg of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide was refluxed in 5 ml acetone. 80 mg pyridine hydrochloride was added. The mixture was refluxed for 20 h. The mixture was allowed to cool to room temperature and then filtered and the crystals were washed with acetone. Yield 241 mg.

Example 6

Preparation of an ethanol solvate

200 mg of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide was refluxed in 4 ml ethanol until dissolved. 80 mg pyridine hydrochloride was added. The mixture was allowed to cool to room temperature, crystallisation starts. The stirred suspension was then left at room temperature over night. The mixture was then filtered and the crystals were washed with ethanol. Yield 97 mg.

Example 7

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form D

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride (0.5 g, 0.001 mol) was solved in a mixture of methanol (5 ml) and water (5 ml) at 60°C. An additional amount of water (2 ml) was added and the mixture was left for 3 days at room temperature. The crystals were filtered off and washed with methanol (30%) and dried at room temperature. Yield: 0.21 g

Example 8

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride was dissolved in methanol and left without cover at 4°C. After three days methanol had evaporated and crystals had formed.

Example 9

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride was dissolved in methanol and water (1:1) and left without cover at 4°C. After seven days crystals had formed in the solution.

CLAIMS

1. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt in a substantially crystalline form.

2. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form A		**Form A**		**Form A**	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
11.3	vs	4.86	m	3.41	m
10.1	s	4.73	w	3.33	m
9.7	vs	4.58	w	3.14	m
9.4	s	4.44	m	3.08	m
8.3	m	4.29	w	3.01	w
7.1	vs	3.99	w	2.90	w
6.5	m	3.95	m	2.76	m
5.9	m	3.86	m	2.70	w
5.5	s	3.70	m	2.64	m
5.3	m	3.54	m	2.55	w
5.1	w	3.45	s	2.50	w

3. Di [2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrochloride salt form B according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form B		**Form B**		**Form B**	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
14.2	s	5.8	s	3.93	s
11.2	m	5.7	s	3.80	s
10.1	s	5.6	s	3.68	vs
9.4	vs	5.5	s	3.66	vs
8.9	vs	5.4	m	3.58	vs
8.5	vs	5.1	s	3.38	vs
7.9	m	4.59	m	3.23	vs
7.2	vs	4.43	vs	3.11	s
6.8	vs	4.38	s	3.03	m
6.5	vs	4.33	vs		
6.0	vs	4.26	s		

4. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form C according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form C		**Form C**		**Form C**	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
13.1	vs	5.0	m	3.57	m
8.3	vs	4.59	s	3.52	m
8.0	s	4.39	m	3.43	s
7.1	s	4.27	m	3.40	s
6.8	m	4.14	m	3.32	s
6.6	vs	3.95	s	3.27	m
5.9	w	3.81	m	3.06	m
5.8	m	3.71	m	2.95	m
5.2	w				

5. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form D according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form D		Form D		Form D	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
16.0	vs	5.3	w	3.56	m
14.1	w	5.2	m	3.44	w
9.5	m	4.84	m	3.39	m
8.5	m	4.65	m	3.27	w
7.8	s	4.23	w	3.21	w
7.7	m	4.11	m	3.01	w
7.5	w	4.00	w	2.98	w
7.1	m	3.88	m	2.80	w
6.8	m	3.83	m	2.74	w
6.5	w	3.72	w	2.67	w
6.0	m	3.62	s	2.61	w

6. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form E according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form E		Form E	
d value (Å)	Relative intensity	d value (Å)	Relative intensity
14.0	vs	4.31	w
13.2	s	4.15	vw
9.0	vw	4.00	vw
8.3	w	3.51	w
7.9	m	3.43 (3.433)	m
7.5	vw	3.43 (3.426)	m
7.0	vs	3.17	vw
6.6	m	2.99	vw
5.3	w	2.80	vw
5.0	vw	2.75	vw
4.68	w	2.34	w

7. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form F according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form F		Form F		Form F	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
12.7	m	5.1	m	3.46	m
11.0	vs	4.72	w	3.41	m
10.1	vs	4.44	w	3.38	m
8.3	s	4.30	w	3.32	s
7.0	m	4.16	s	3.22	m
6.8	m	4.12	m	3.05	m
6.7	m	4.09	m	2.77	m
6.0	m	3.97	w		
5.5	s	3.88	m		
5.4	s	3.68	m		
5.3	m	3.61	m		

8. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt n-propanol solvate according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

n-propanol solvate		**n-propanol solvate**		**n-propanol solvate**	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
12.6	vs	4.34	w	3.24	s
9.8	vs	4.00	m	3.11	m
9.7	vs	3.94	s	2.77	m
6.7	vs	3.80	m	2.70	m
6.5 (6.55)	s	3.70	m	2.60	w
6.5 (6.48)	m	3.66	s	2.55	w
6.3	s	3.58	m	2.44	w
4.93	vs	3.52	m	2.30	w
4.84	m	3.44	m		
4.54	m	3.34	m		

9. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt acetone solvate according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

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Acetone solvate		**Acetone solvate**		**Acetone solvate**	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
12.6	m	4.34	w	3.23	m
9.8	vs	4.25	w	3.16	w
7.9	m	4.20	w	3.08	w
6.6	s	4.07	m	3.02	m
6.5	m	3.97	m	2.89	w
6.3	m	3.92	m	2.85	w
5.4	w	3.79	w	2.70	m
5.2	w	3.71	w	2.65	w
5.1	m	3.67	s	2.59	w
4.90	s	3.59	w	2.52	w
4.80	m	3.50	m	2.48	w
4.57	w	3.41	m	2.44	w
4.53	m	3.34	m	2.42	w

10. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt ethanol solvate according to claim 1, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Ethanol solvate		Ethanol solvate		Ethanol solvate	
d value (Å)	Relative intensity	d value (Å)	Relative intensity	d value (Å)	Relative intensity
12.5	vs	4.54	m	3.40	m
10.4	m	4.22	m	3.31	s
9.7	vs	4.04	m	3.20	s
7.8	m	4.00	m	3.15	m
6.6	vs	3.95	m	3.09	m
6.4	m	3.89	s	3.06	m
6.3	m	3.76	m	2.84	m
5.2	m	3.69	m	2.73	m
5.044	m	3.62	vs	2.70	m
4.87	s	3.55	m	2.57	m
4.77	m	3.48	m	2.51	m

11. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A as defined in claim 2 comprising the steps of:

a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or a mixture of any form in ethyl acetate,

b) allowing the solution or suspension to crystallize, and

c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form A thus obtained.

12. A process for the preparation of di [2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrochloride salt form B as defined in claim 3 comprising the steps of:

a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-

imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or a mixture of any form in acetonitrile,

b) allowing the solution or suspension to crystallize, and

c) isolating the di [2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrochloride salt form B thus obtained.

13. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form C as defined in claim 4 comprising the steps of:

a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or a mixture of any form in butanol

b) allowing the solution or suspension to crystallize, and

c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form C thus obtained.

14. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form D as defined in claim 5 comprising the steps of:

a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or a mixture of any form in methanol/water (5:7, by volume)

b) allowing the solution or suspension to crystallize, and

c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form D thus obtained.

15. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form E as defined in claim 6 comprising the steps of:

a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or a mixture of any form in methanol,

b) allowing the solution or suspension to crystallize, and

c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-

carboxamide hydrochloride salt form E thus obtained.

16. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form F as defined in claim 7 comprising the steps of:
a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or a mixture of any form in methanol/water (1:1, by volume)
b) allowing the solution or suspension to crystallize, and
c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt form F thus obtained.

17. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt n-propanol solvate as defined in claim 8 comprising the steps of:
a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or a mixture of any form in n-propanol,
b) allowing the solution or suspension to crystallize, and
c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt n-propanol solvate thus obtained.

18. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt acetone solvate as defined in claim 9 comprising the steps of:
a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or a mixture of any form in acetone,
b) allowing the solution or suspension to crystallize, and
c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt acetone solvate thus obtained.

19. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt ethanol solvate as defined in claim 10 comprising the steps of:

a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt of any form, or a mixture of any form in ethanol,

b) allowing the solution or suspension to crystallize, and

c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt ethanol solvate thus obtained.

20. A process according to any of claims 11 to 19, characterized in that seeds are added to the solution/suspension to induce crystallization.

21. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt prepared according to any of claims 11 to 20.

22. The use of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride salt as defined in any of claims 1 to 10 in therapy.

23. A pharmaceutical formulation comprising 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide as defined in any of claims 1 to 10 in admixture with at least one pharmaceutically acceptable excipient.

24. The use of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride as defined in any of claims 1 to 10, as active ingredient in the manufacture of medicament for use in treatment of gastrointestinal disorders.

25. A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride as defined in any of claims 1 to 10, to a patient suffering from gastrointestinal disorders.

Figure 1. An X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride form A measured with variable slits.

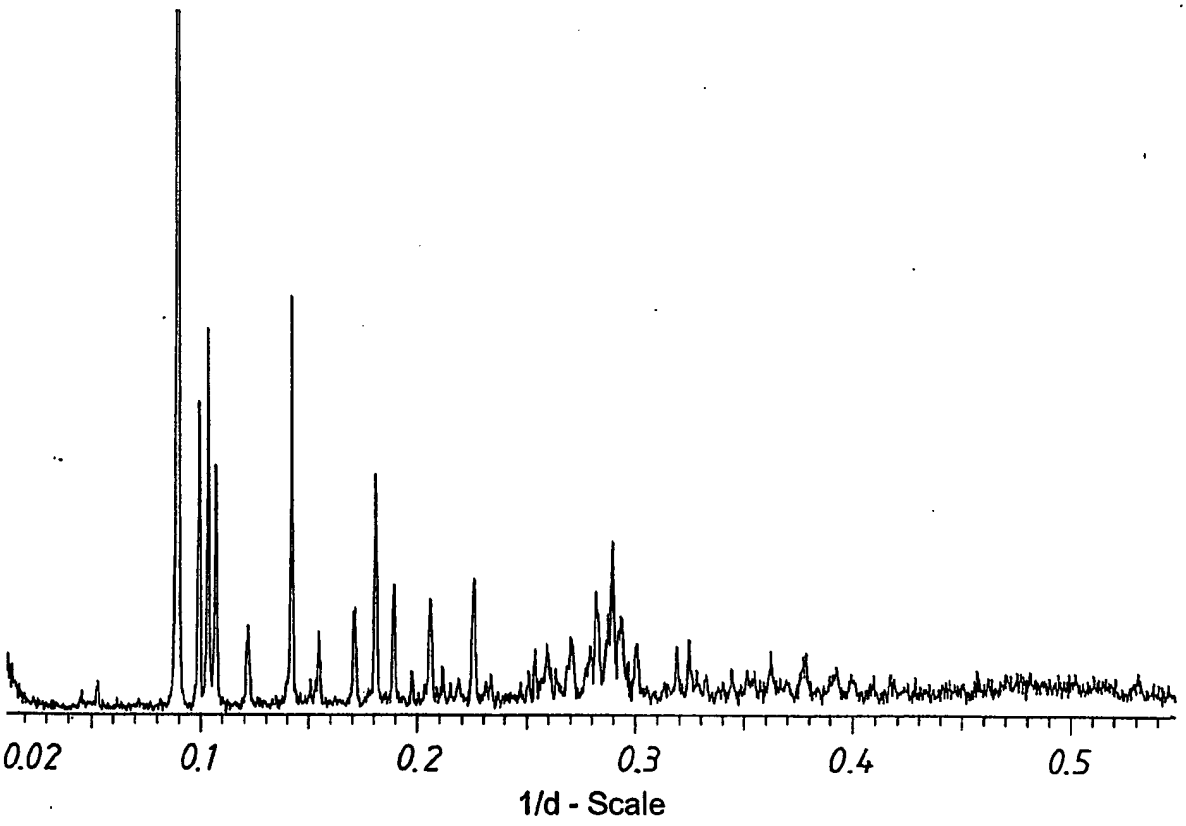


Figure 2. An X-ray powder diffractogram of di [2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide] hydrochloride form B measured with variable slits.

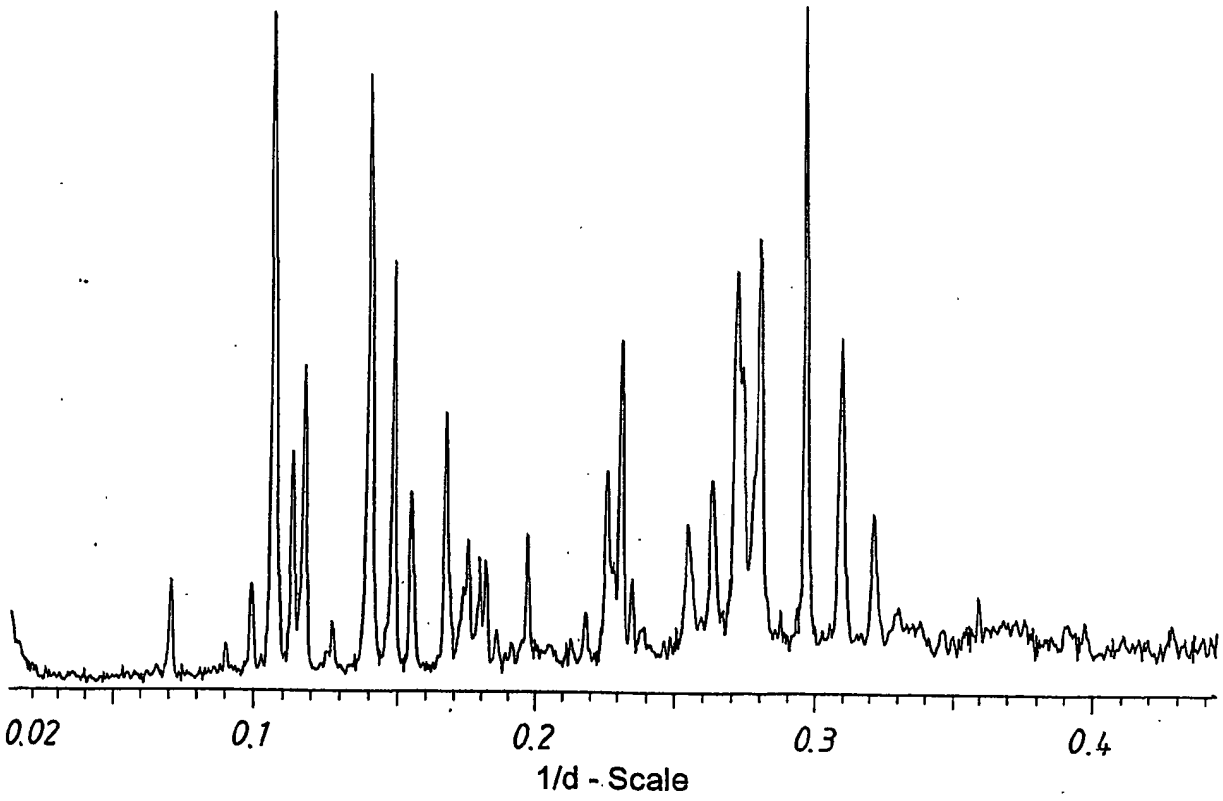


Figure 3. An X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride form C measured with variable slits.

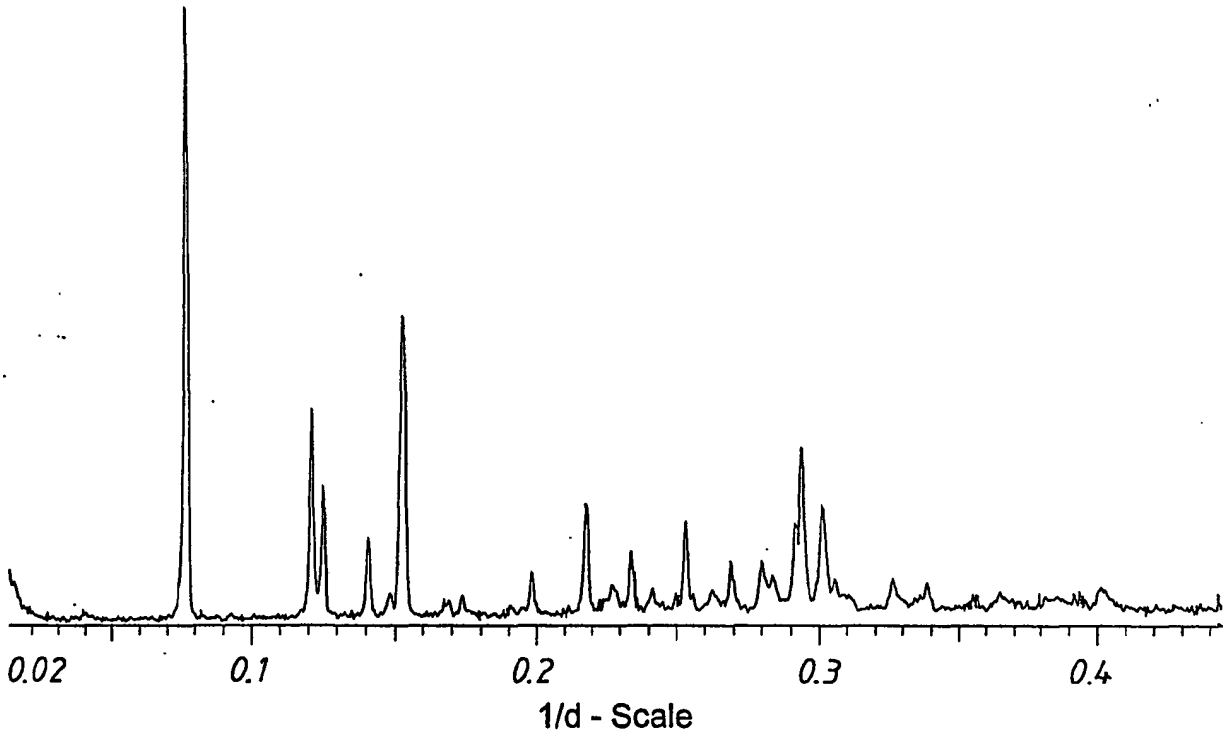


Figure 4. An X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride form D measured with variable slits.

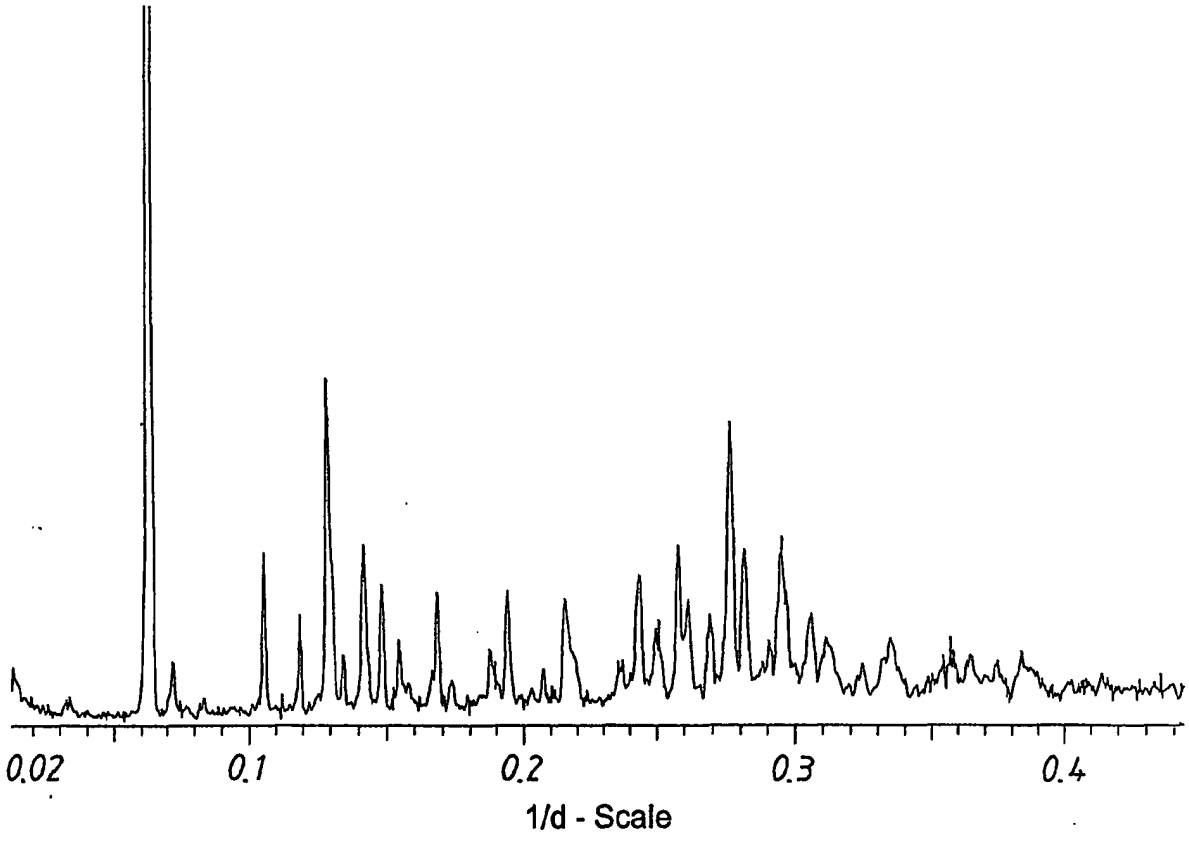


Figure 5. An X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride form E measured with variable slits.

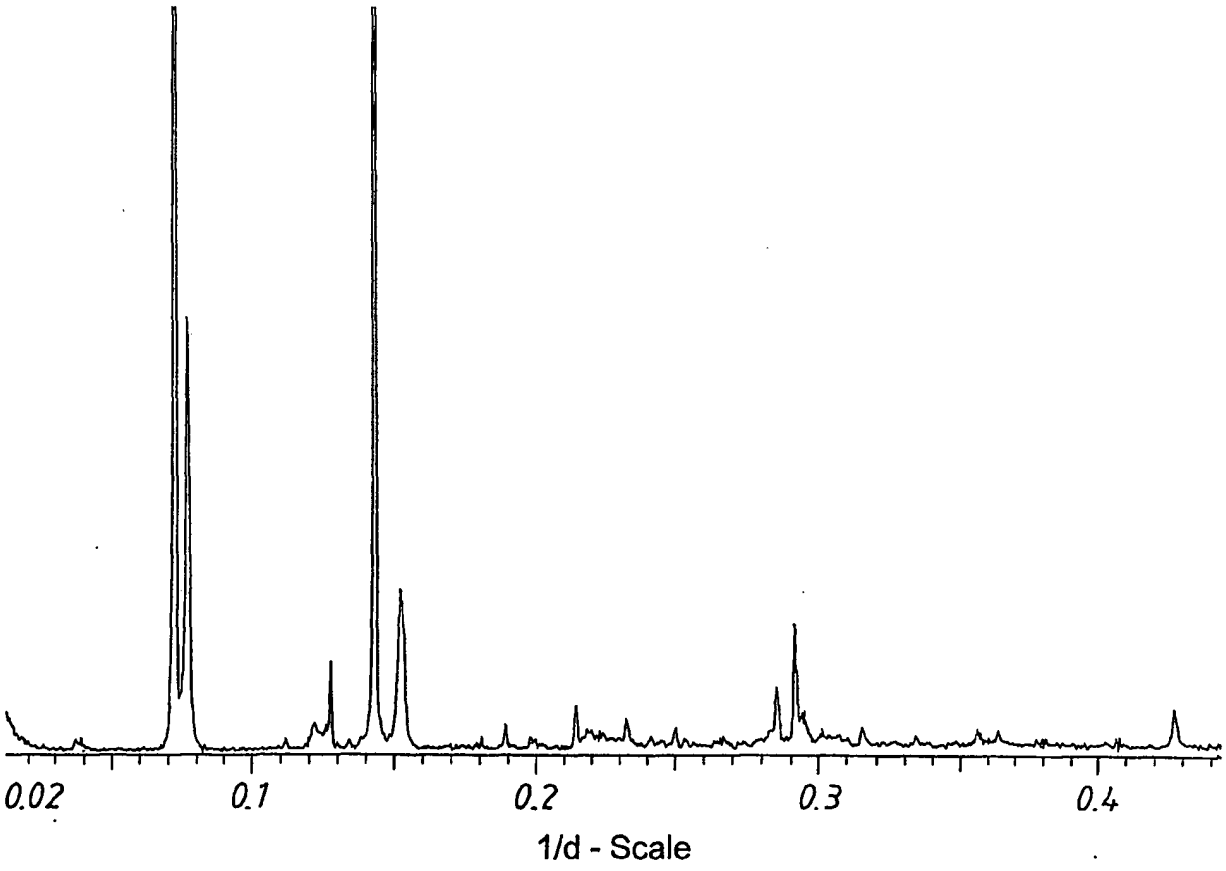


Figure 6. An X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride form F measured with variable slits.

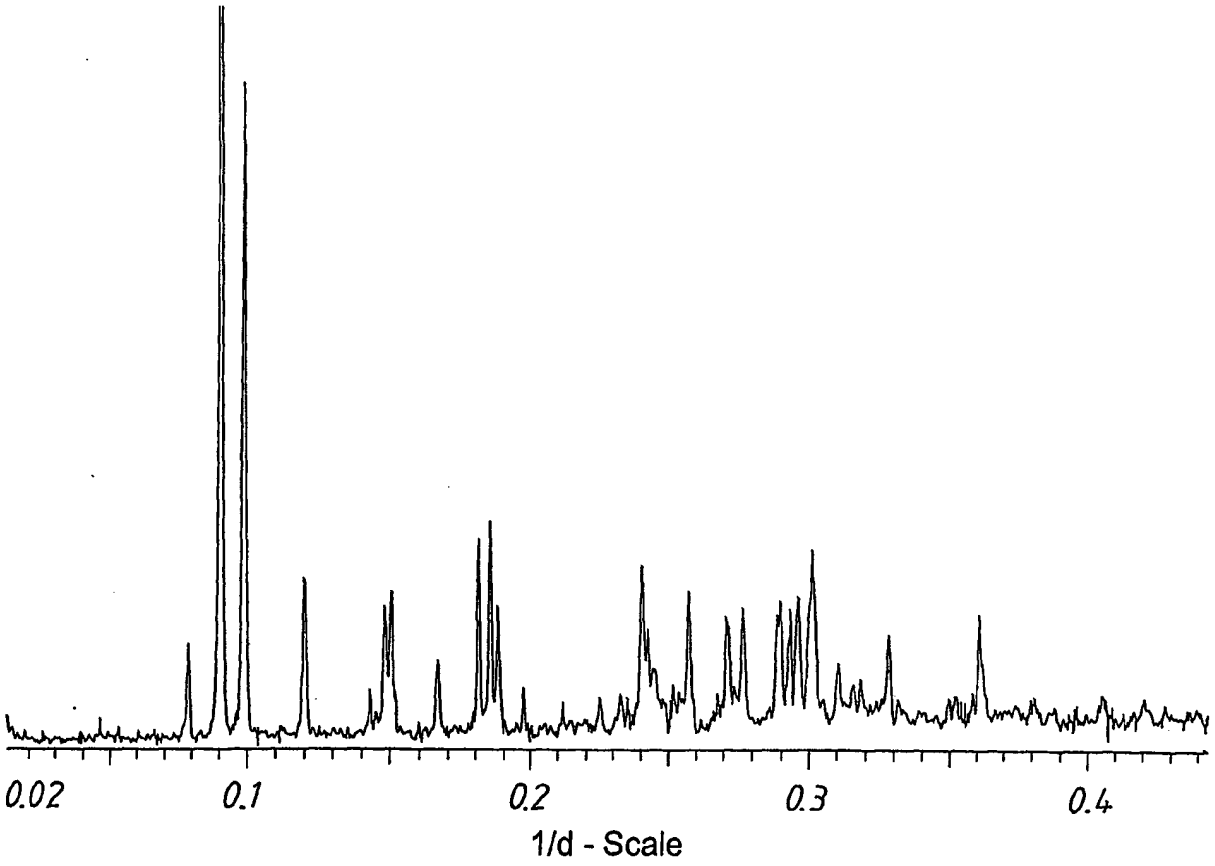


Figure 7. An X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride n-propanol solvate measured with variable slits.

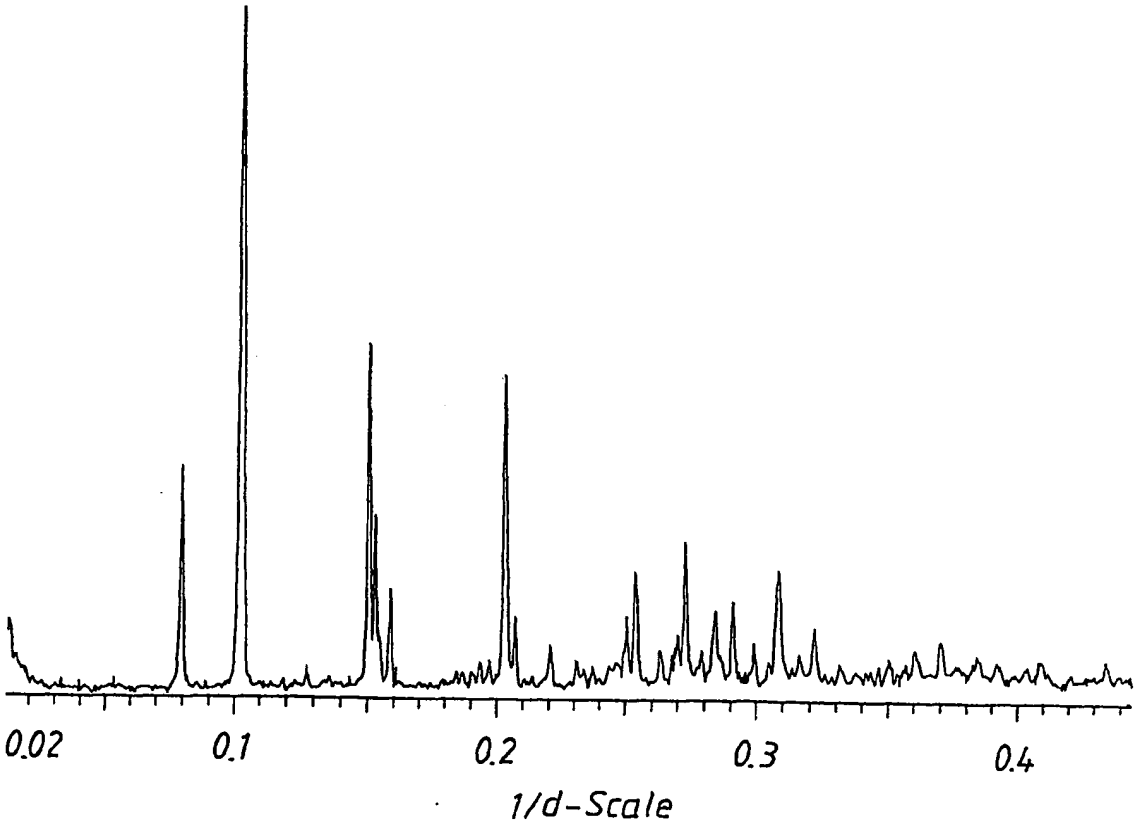


Figure 8. An X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride acetone solvate measured with variable slits.

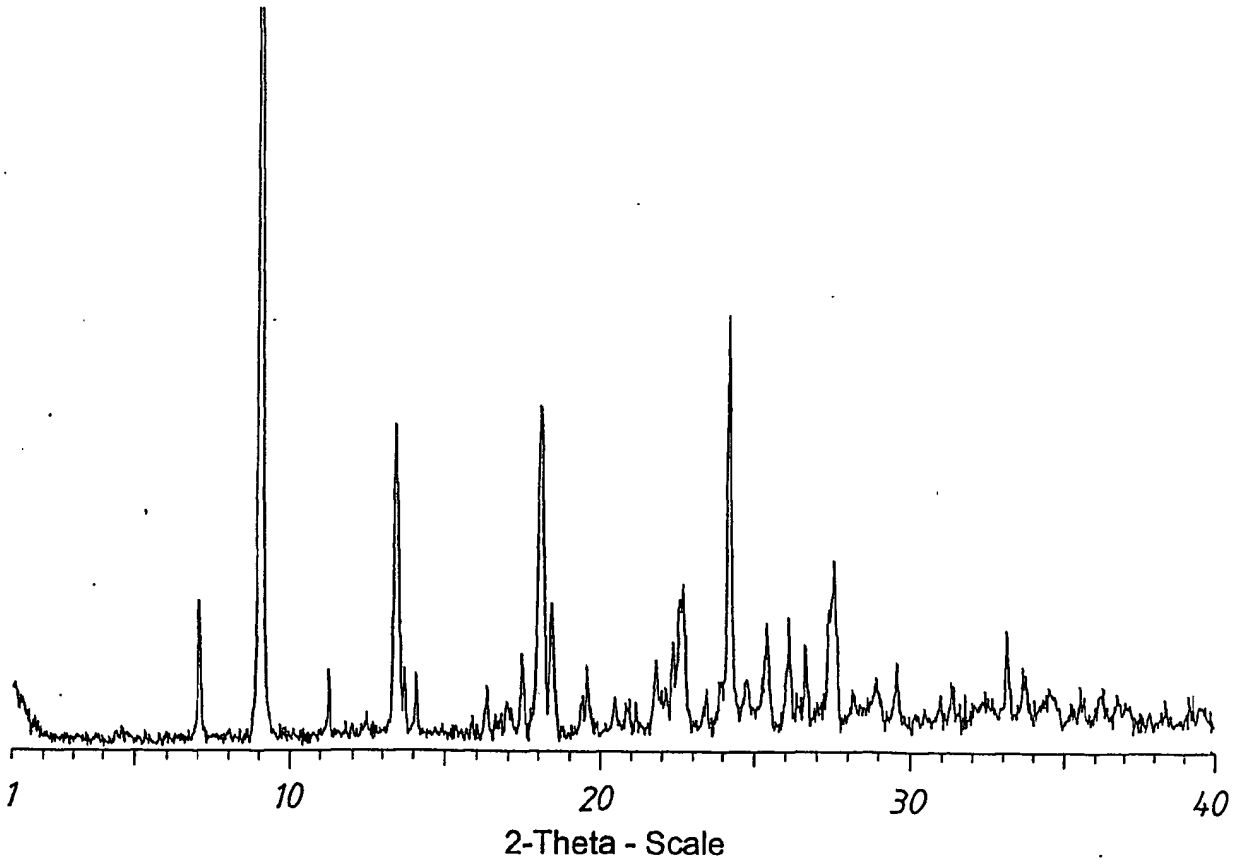
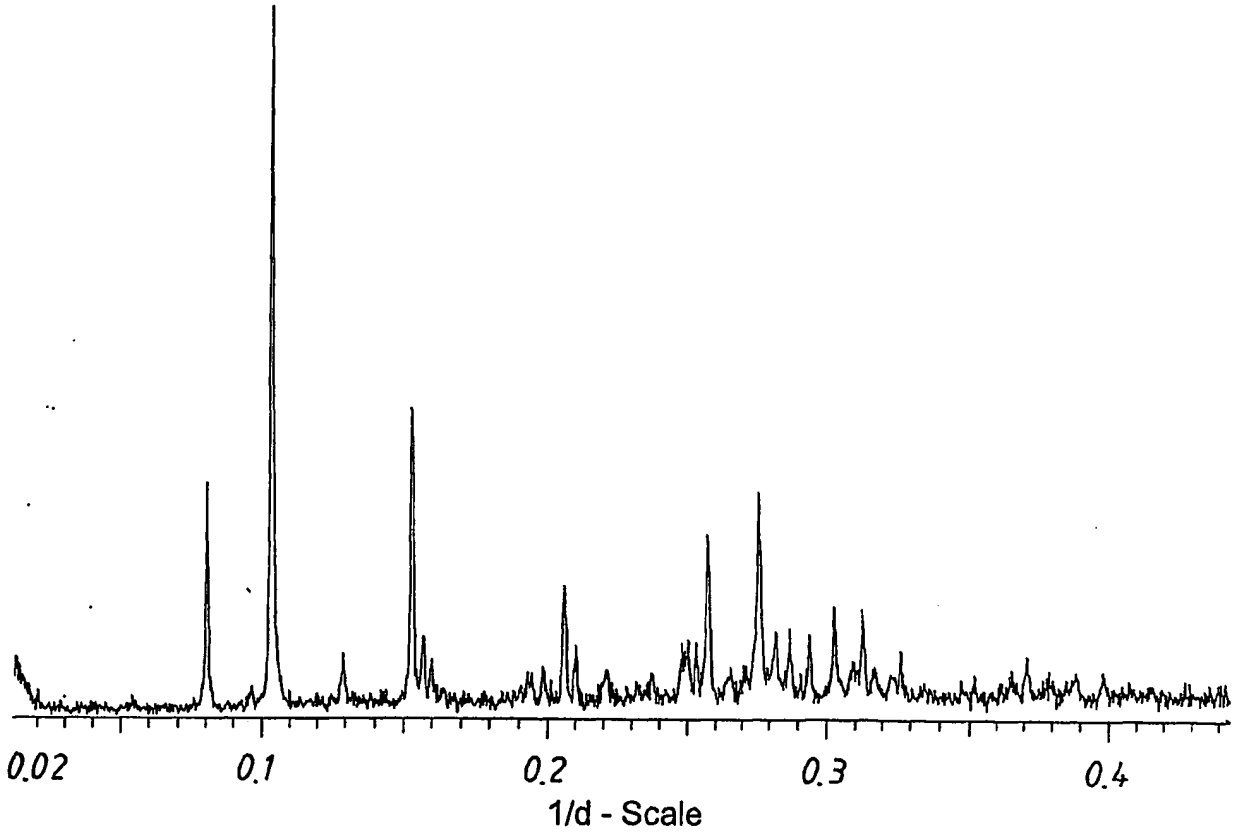


Figure 9. An X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide hydrochloride ethanol solvate measured with variable slits.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00164

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/4188, A61K 31/437, C07D 471/04, A61P 1/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM ABS. DATA, BIOSIS, EMBASE, MEDLINE, EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9955705 A1 (ASTRA AKTIEBOLAG), 4 November 1999 (04.11.99), page 36, example 2.5; abstract; claim ---	1-21
X	WO 9955706 A1 (ASTRA AKTIEBOLAG), 4 November 1999 (04.11.99), page 24, example 1.4; abstract; claim --- --------	1-25

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2002	14 -05- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Per Renström/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00164

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 22, 25
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box I.1

Claim 22 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

Claim 25

See PCT Rule 39.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/05/02

International application No.
PCT/SE 02/00164

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 6313137 B	06/11/01
		WO 9955706 A	04/11/99

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/05/02

International application No.
PCT/SE 02/00164

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